PREVALENCE OF CUTANEOUS SIDE EFFECTS OF LITHIUM THERAPY IN BIPOLAR AFFECTIVE DISORDER PATIENTS- A PROSPECTIVE OBSERVATIONAL STUDY

Submitted

BY

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Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI,

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE IN PSYCHIARY

Under the guidance of

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COIMBATORE – 2015

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**Prevalence of cutaneous side effects of lithium therapy in Bipolar affective disorder patient- a prospective observational study.**" is a bonafide and genuine research work carried by me under the guidance of Dr. I. SYED UMMAR, Associate Professor, Department of Psychiatry, PSGIMS & R, Coimbatore.

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June 16, 2014

To
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Ref.: Proposal titled: *"Incidence of cutaneous side effects with lithium therapy in BPAD patients - a prospective cohort study"*

Sub.: Ethics Committee Approval for the study

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 26th May, 2014 in its full board review meeting held at College Council Room, PSG IMS&R, between 2.00 pm and 4.45 pm, and discussed your application to conduct the study entitled:

"Incidence of cutaneous side effects with lithium therapy in BPAD patients - a prospective cohort study"

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent forms (Ver 1.1)
4. Data Collection Tool
5. CV
6. Budget

The members who attended the meeting at which your study proposal was discussed are as follows:

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12	Dr. Y.S. Sivan	Ph D	Social Scientist (Sociology)	Male	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mrs. K. Uma Maheswari	M Sc, M Phil. B Ed	Botany	Female	No	Yes
15	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

After due consideration, the committee has decided to approve the above proposal.

The approval is valid for one year.

We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

We hereby confirm that neither you nor any of your study team members have participated in the voting/ decision making procedure of the committee. The members of the committee who have participated in the voting/ decision making procedure of the committee do not have any conflict of interest in the referenced study.

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

PIs are required to send progress reports (in the form of an extended abstract with publications if any) to the IHEC every six months (and a month before expiry of approval date, if renewal of approval is being sought).

Request for renewal must be made at least a month ahead of the expiry of validity along with a copy of the progress report.

16.6.14

Dr S Bhuvaneshwari
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PREVALENCE OF CUTANEOUS SIDE EFFECTS OF LITHIU
IN BIPOLAR AFFECTIVE DISORDER PATIENTS

ABSTRACT

BACKGROUND:

The prevalence of lithium induced skin reactions ranges from 3- 34 % in few studies a is 45% another study. Cutaneous side effects occurs when the dose of lithium 800-120 on therapeutic level (0.8 -1.2meq/l) and when lithium is given for the longer duration (more than 1 year).

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AIM OF THE STUDY:

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ABSTRACT

BACKGROUND:

The prevalence of lithium induced skin reactions ranges from 3- 45% in various studies. Cutaneous side effects occurs when the dose of lithium 800-1200, on therapeutic level (0.8 -1.2meq/l) and when lithium is given for the longer duration (more than 1 year).

OBJECTIVES OF THE STUDY:

1. To assess the prevalence of skin reactions in Bipolar affective disorder (BPAD) patients on lithium **2**.To evaluate the relationship between the dosage of lithium and cutaneous side effects **3**.To assess the relationship between serum lithium level and cutaneous side effect. **4**.To evaluate the duration of lithium therapy and cutaneous side effects.**5**.To assess the reduction or stoppage of dose of lithium has any change in the course of cutaneous side effects.**6**.To assess the course of pre-existing skin reactions, when patient is initiated on lithium therapy.

METHODOLOGY:

Prospective observational study. Both Inpatient and outpatients with bipolar affective disorder on lithium therapy were recruited. They were assessed with initial semi-structured proforma and dermatologist opinion obtained for patients who developed cutaneous side effects. They were followed up for once a month for 6 months and once in 2 months thereafter for 1 year.

RESULT:

The prevalence of lithium induced skin reactions was **38.46%.** .Our study has shown different dosage and serum lithium level doesn't correlate statistically with lithium induced skin reaction but longer the duration more is the chance for lithium induced cutaneous side effects.

CONCLUSION:

Prevalence of Lithium induced skin lesions continues to be high. Clinician should educate the patient before initiating lithium to improve the attrition rate. Prevalence doesn't vary between the dosage and serum lithium level, but varies with duration of lithium therapy. Hence, the clinician need not be ambivalent about reducing the dose but should be cautious on prolonged treatment.

INTRODUCTION:

Lithium has been used in the treatment of mood disorders for more than five decades. Inspite of its narrow therapeutic index and multiple systemic side effects lithium remains the golden standard treatment for bipolar affective disorder. Various studies have been done to find the relationship between the dose of lithium carbonate, serum lithium levels, duration of therapy, and clinical response.

Lithium is a cheaper and easily available molecule compared to other mood stabilizers approved by Food and drug administration (FDA). Apart from its mood stabilizing effect it's preferable among mood stabilizer for its anti-depressant and anti-suicidal properties.

The dosage of lithium therapy is individualized. It is usually started with the low divided doses and is titrated up based on the serum lithium levels to minimize the side effects. Serum lithium level is monitored once a week until a concentration of 0.8-1.2meq/l is reached. [(1)] Inspite of recommended maintenance of lithium considered being 0.5-0.8 meq/l; it is preferable to continue the same dose of lithium that was considered for acute episode.

Previous studies has recommended a therapeutic range from 0.7 to1.2 meq/l as Lithium was found to be ineffective at levels below 0.9meq/l. They also have reported that no therapeutic advantage was noted when the serum lithium level is above 1.3meq. But with levels more than 1.4meq/l there were severe side effects [(2)]. In previous studies Lithium induced cutaneous side effects occurred mostly within therapeutic range and few above the therapeutic range [(3, 4)].

With the lithium level of 1.5-2meq/l mild to moderate intoxication occurs characterized by gastrointestinal symptoms like vomiting abdominal pain, dryness of mouth, and neurological symptoms are ataxia, dizziness, slurred speech, nystagmus, lethargy or excitement and muscle weakness.

Serum lithium levels between 2 to 2.5 meq/l can cause moderate to severe intoxication characterized by blurred vision, muscle fasciculation, clonic limb movement, hyperactive deep tendon reflex, choreoathetoid movements, convulsion, delirium, syncope, stupor, coma and circulatory failure (low BP, cardiac arrhythmias and conduction abnormalities). GI symptoms like anorexia and persistent vomiting.

Severe lithium intoxication occurs with the level > 2.5meq/l characterized by generalized convulsion, oliguria, renal failure and death [5]. > 4meq/l intoxication requires dialysis as treatment.

Few studies have shown that even lower lithium levels (0.4-0.6meq/l), can cause cutaneous side effects compared to therapeutic range [3].

Studies have shown that longer the duration of Lithium therapy, more is the chance of developing side effects [4, 9]. However skin reaction may occur as early as within few days of starting Lithium therapy.

Lithium has been the focus of numerous investigations for its side-effects. Most of the studies were concerned with the systemic side effects like hypothyroidism, hyperthyroidism, hyperparathyroidism, nephrogenic diabetic insipidus, nephritic syndrome, renal tubular acidosis, cardiac bradyarrhythmia, heart block, tremors, diarrhoea and convulsions. Though Lithium is notorious to cause cutaneous lesions [6] the literature on skin disorders secondary to lithium therapy is limited.

Lithium is known to cause multiple cutaneous side effects. The most common cutaneous side effects associated with lithium are acneiform eruptions and psoriasiform eruption [8]. It has been known to cause psoriasis and also exacerbate the pre-existing psoriasis .It causes specific manifestations like acneiform eruptions, seborrheic dermatitis, and follicular keratitis.

Other cutaneous manifestations includes mucosal and vaginal ulceration, oedema, purpura, lupus erythematosis like syndrome, urticaria, pre-tibial ulceration,dermatitis herpetiformis, eczema, exfoliative dermatitis, folliculitis, alopecia, allergic vasculitis, hidradenitis suppurativa, lichenoid stomatitis, exacerbation of Darrier's disease, palmoplantar hyperkeratosis with icthyosiform features, increased growth of wart, mycosis fungoidosis, increased growth of warts and hair loss[7,9].

In previous study, females showed increased incidence of cutaneous side effects compared to males [8]. In other study secondary cutaneous side effects are more common with males [8].The most distressing lithium induced cutaneous side effects being psoriasis and it has been associated with the increased risk of suicide and substance use .These disturbances in the self image affects their social, occupational and interpersonal functioning. This may contribute to the risk of non-compliance among lithium treated patients [10].

The prevalence of lithium induced skin reactions is reported to range from 3 to 34 %[8]. In another study the prevalence of lithium induced skin reactions is reported to be 45 %[9]. There are very few studies on lithium induced skin reactions and chances of discontinuation of therapy because of adverse skin reactions persist in clinical settings.

We did a pilot project retrospectively based on the case records with sample of 30 BPAD patients where the prevalence of lithium induced skin reaction was 20% .We had concluded that higher the dose of lithium increase in the prevalence of skin reaction. The prevalence was also high in sub-therapeutic (0.5-0.8meq/l) serum lithium level.

Hence we planned to do a prospective observational study and are unique of its kind as there is no published study on the relationship between cutaneous side effect with lithium dosage, duration and serum lithium level.

REVIEW OF LITERATURE:

There is a paucity of literature on lithium induced skin reactions. Most common conditions seen with lithium therapy are acne and psoriasis.

Lithium and maculopapular eruptions:

Maculopapular eruption is a type of rash characterized by an erythematous spot with small, flat red area covered raised bumps.

Callaway et al in 1968 had reported 5 cases of lithium induced maculopapular eruptions. Of which three had developed lesions in the whole body and one had developed in the legs. Three had pre-tibial ulceration and 3 were associated with pruritis. [(11)] All occurred within 3 weeks of duration of lithium therapy and with the levels of 0.53-1.5meq/l. maculopapular eruptions and cutaneous ulcers were cleared after discontinuation of lithium in 2 cases and after reduction of dosage with the treatment of topical applicants in other case

Posey had described a case that had developed pruritic papular dermatitis on pressure point in young female. These lesions resemble dermatitis herpetitiformis. It resolves when the dose of lithium is tapered to the lithium level of 0.8-1.2 meq/l and on treatment with sodium sufoxone[(12)].

Meinhold et al had described a diffuse, erythematous maculopapular rash in volunteers with no past episode of any dermatological complaints or allergies. It occurs with the dose of 600mg of lithium on two different occasions [13].

In general lithium induced maculopapular eruptions are generalized and pruritic and it occurs due to delayed hypersensitivity reaction. It resolves with or without stopping or reducing the dose of lithium and with the treatment of topical applicants.

Lihtium and Acne, Acneiform eruption:

Acneiform eruptions are papulopustular, nodular or cystic dermatosis which usually lack comedones.

Kusumi in1971 reported a patient who had developed acneiform eruption within few days of starting lithium therapy. It resolved on discontinuing lithium. They again developed acneiform eruptions on reinstitution of lithium. Case reports by Oei and bour, 1978 show that lithium is found to exacerbate pre-existing acne.

Yoder in 1975 described acneiform eruptions due to lithium. Acneiform eruptions are characterized by monomorphic pustules on an erythematous base. Most commonly it occurs in the extremities. Histological examination of severe acneiform eruptions over the extremities reveals they were suggestive of folliculitis. [(14)]

Aldoroty and Levine had described a patient on lithium that developed an acneiform eruptions over face .It occurs after 2 weeks of lithium therapy with serum lithium level of 0.5-0.6 me/l. lesions were treated with minocyclin and tetracycline despite worsening occurred. Improved on reduction of dosage and completely remitted on stoppage of lithium.

Naveen Kansal had described the mechanism under which lithium causes skin reaction. They postulated that lithium causes alteration in the calcium homeostasis by modulating the second messenger system such as adeny cyclase and inostol monophosphatase pathways. The resulting lower intracellular calcium levels leads to increased proliferation of keratinocytes and increases the inflammatory reactions of polymorphonuclear leukocytes. Acneform eruptions usually cleared with the use of topical retinoids[(15)].

Lithium and Psoriasis:

Psoriasis are chronic cutaneous problem characterized by thick white silvery or red patches, which most often appears on the knees, elbows, scalp, extremities or lower back.

The association of lithium with psoriasis was described by carter in 1972.The incidence of lithium induced psoriasis has reported to be 1.8 to 6%. Lithium causes exacerbation of pre-existing psoriasis, triggers psoriasis in no family or past history of psoriasis and induces psoriasis in unaffected area of psoriatic patients.

Bakker and Pepplinkhuizer et al in 1976 had described case reports on psoriasis and its association with lithium. 23 cases were reported of which 13 had pre-existing psoriasis and family history of psoriasis. They reported that after initiating lithium therapy, pre-existing psoriasis was aggravated and the response to previous effective treatment had become poor. 15 cases were reported to have developed psoriasis for the first time after initiating lithium therapy. (12)

In a case report in 2006, a 60 years old female had developed a red maculopapular rash within 6 days of initiation of lithium therapy. Serum lithium level was found to be within therapeutic range. Females are more prone to develop psoriatic lesions and were usually within the first year. In this case they temporally correlated the duration of therapy and the onset of rash. (11, 16)

Studies shows patient develops psoriatic lesions on therapeutic serum lithium level (17). The relationship with the dose of lithium and the appearance of psoriasis is not yet clear. Most of the

studies have noticed that there is no relationship with the dose of lithium and the appearance of psoriasis [18]. But few study reports a dose-dependent relationship of lithium and development of psoriasis. [19]

The latency period between the development of psoriatic lesions and the initiation of lithium treatment ranges from a weeks to several months [20].These latency periods are classified as short (< 4 weeks), medium (4 weeks- 12 weeks) and long (> 12 weeks). The latency period is shorter for exacerbation of pre-existing psoriasis than for induction of new psoriasis.

The clinical manifestation of lithium induced psoriasis and idiopathic psoriasis are similar. The most common manifestation is plaque type lesions mostly in the scalps which gradually spreads to the trunk and extremities and are mostly resistant to treatment. But other manifestations are generalized psoriasis, pustular psoriasis, palmoplantar pustulosis, erythroderma, non specific psoriasiform dermatitis, scalp psoriasis,finger nail abnormality, psorasiform dermatitis and psoriatic arthropathy[21]. Psoriatic nails are characterized by the yellow, opaque, roughening and pitting of nails.

The mechanism of lithium induced psoriasis is not known. Lithium causes decrease in cyclic adenosine monophosphate which results in low levels of intracellular calcium leads to increased proliferation of keratinocytes, affect terminal differentiation, enhanced chemotaxis, and phagocytic activity of leukocytes [22, 23].

Another hypothesis is that “inositol depletion hypothesis” that lithium causes depletion of inositol monophosphatase results in lower level of intracellular calcium. This is evident by the supplementation of inositol reverses the psoriasis caused by lithium.

Recent studies shows that lithium is involved in cytokine dysregulation (interleukin 2, tumor necrotic factor alpha and interferon beta) and it may play an important role in the pathogenesis of psoriasis.

Recent studies showed that inositol use in treating lithium induced psoriasis. Dietary inositol does not cross the blood brain barrier and does not affect the effect of lithium as mood stabilizers [(24)]. It is evidenced by improvement in the Psoriasis Area and severity index (PASI) scale.

Another study showed that omega -3-fatty acid of around 6g/day was useful in acute lithium induced psoriasis [(25)].

Lithium induced psoriasis are resistent to treatment and are managed with topical steroids, vitamin D analogues, oral retinoids, PUVA (psoralen and ultraviolet A) therapy, and methotrexate[(26)].Even treatment resistant psoriasis warrants change of mood stabilizers

Lithium and systemic lupus erythematosis:

Systemic lupus erythematosis is a chronic inflammatory disease that has relapsing and remitting course.

Antonov et al had described that lithium is suggested to induce lupus erythematosis. Lithium induced lupus was more common among females and among adolescence (20-40 years). The mechanism of lithium induced SLE is not yet clear [(27)].

Cell mediated immunity is affected in systemic lupus erythematosis. The blood sample of SLE patients was found to have low interleukin 2 level and these low levels correlated with the severity of illness. Study showed that in vitro incubation of T-cells with lithium augment interleukin-2 production. Lithium is believed to increase the cytosol inositol triphosphate level and increase impaired intracellular transduction in T cells.

Lithium and alopecia:

Orwin 1983, Mc Creadie and Morrison 1985, reported 2 case studies in which they had described 12-17% of patient's complaints of hair loss most commonly among females [28]. They had described that hair loss to be occurring within 4 months of starting lithium therapy and hair loss is reversible on withdrawal of lithium. In some studies it is reported to have 12-19% hair loss. [29]

Yassa and Ananth 1983, they had described evidences for the reversibility of hair loss on withdrawal of lithium. Controversial reports in Some studies states that hair fall subsides even during the course of lithium therapy [30].Jefferson et al 1979, had demonstrated the cause/ effect relationship, where rechallenging of lithium therapy causes hair loss .

Mortimer and Dawber et al had described that hair loss occurs within therapeutic range of lithium therapy.

The exact etiologies for hair loss are unknown. It has been hypothesized that lithium gets concentrate in the hair follicles. It affects both the growth and size of the hair. But no pathology was found in hair samples on electron microscopy. Other hypothesis are hypothyroidism occurs during lithium therapy are known to cause hair loss. Causal relationship has been associated with hair loss and hypothyroidism. But still has not been proven yet. Monitoring thyroid function test is necessary .Corrections of thyroid status results in reversibility of alopecia [31, 32, and 33].

A three year follow up study on lithium cases reported about 12% incidence of alopecia [34].23% reported their hair to become straighter and 19% to have thinning of hair. It causes alopecia usually within 4-6 months period of lithium therapy. **Vestergaard p et al in 1980** described that Scarcity of all body hair occurs if the person had pre-existing alopecia areata.

Reports were also found on combination of both hair loss and severe acneiform eruptions due to lithium carbonate. It occurred during a period of 3 months of therapy

Lithium and folliculitis:

Folliculitis is defined based on the histological features with the presence of inflammatory cells within the hair follicle creating follicular based pustules.

Lithium induced folliculitis are usually asymptomatic and are distributed in the extensor surface of the forearm and is due to inflammatory reaction. It occurred after longer duration of lithium and resolved spontaneously even with the therapy. Histological reports revealed follicular dilatation with chronic inflammatory infiltrate around the peri-follicular region.

In1983, Sarantidis et al, in his study he had compared both lithium treated patients with the control groups who were on non-neuroleptics. He had described the patients who developed cutaneous conditions because of the lithium or exacerbated due to lithium as secondary cutaneous condition.

In this study they had described that psoriasis and acneiform eruptions were the most common among cutaneous conditions.No significant differences were noted in age among the lithium and the control group. No significant differences were found in the dose, duration of lithium therapy and among family and past history of cutaneous reactions. Females were more common to report secondary cutaneous conditions

Indian studies:

Mohandas et al in his study described the various cuaneous side effects of lithium therapy and the mechanism with which it causes skin reaction. He described the prevalence of alopecia to be 12-19% and occurs on prolonged treatment. The mechanism with which it occurs is not clear but found the lithium aggravates the cutaneous conditions causing neutrophilic infiltration.

Vijay Aithal ,Prakash Appaih in 2015, had described a patient on lithium who developed both acne conglobata and hidradenitis suppurativa (HS). Hidradenitis suppurativa and acne conglobata are rare manifestations with only 3 case reports described so far. In all 3 cases, the serum lithium levels were within the therapeutic range. Patient had taken lithium for longer than 9 years and dose was 400mg. Initially patient had developed acneiform eruption at serum lithium level of 0.7meq/l and later he had developed acne conglobata at level of 0.86meq/l.

Initially it was hypothesized that Hydradenitis suppurativa was due to involvement of apocrine glands. Later it was found to be due to follicular obstruction, folliculitis and cystic dilatation. It is also hypothesized to be caused by neutrophilic chemotaxis which induces an inflammatory cascade [(35)].Hence cutaneous side effects may not correlate with the serum lithium higher than therapeutic level.

K.B Shreedar and et al reported a Case on lithium induced drug hypersensitivity are published in 2015. Lithium induced drug hypersensitivity syndrome is also called as DRESS, Drug rash with eosinophilia and systemic symptoms, DIDMOS – Drug induced delayed multi-organ hypersensitivity syndrome. It is the most severe adverse skin reaction which is characterized by fever,organ involvement and skin rash. They presented with fever, generalized maculopapular rash, glossitis, hepatomegaly, lymphadenopathy and pedal edema within 4 weeks of therapy with the dose of 900mg of lithium and the serum lithium level of 1.12meq/l.It occurs as a result of immunologically mediated reaction in genetically susceptible Individual [(36)].

AIM AND OBJECTIVE OF THE STUDY:

1. To assess the prevalence of skin reactions in Bipolar affective disorder (BPAD) patients on lithium

2. To evaluate the relationship between the dosage of lithium and cutaneous side effects

3. To assess the relationship between serum lithium level and cutaneous side effect.

4. To evaluate the duration of lithium therapy and cutaneous side effects.

5. To assess the reduction or stoppage of dose of lithium has any change in the course of cutaneous side effects.

6. To assess the course of pre-existing skin reactions, when patient is initiated with lithium therapy.

METHODOLOGY:

We recruited both inpatient and outpatient Bipolar affective disorder patient, who were diagnosed based on ICD-10 (international classification of disease) criteria by a qualified psychiatrist and who came to psychiatry department. We recruited patients who were newly started or already were on lithium therapy. We recruited 52 patients by convenient sampling and they were followed up for 12 months. All the patients were recruited after getting written informed consent from the patient's attender and if possible from the patient. If the consent could not be obtained from the patient during initial assessment, it was obtained during subsequent follow up.

Inclusion criteria in our study are people between 18-65 years of age, BPAD patient who were newly started on lithium or already on lithium therapy and who gives written informed consent. We excluded patient on other mood stabilizers and on other medication causing skin reactions (ACE inhibitors, CCB-Amlodipine, diltiazem Fluconazole , Quinine, Terbinafine, Paclitaxel).

Initial Assessment:

Initial assessments were done using initial semi-structured proforma. Sociodemographic details such as age, sex, education status, socio-economic status was collected using a semi structure proforma. Socio-economic status was assessed using Modified kuppusamy's scale.

Baseline information regarding the duration of lithium therapy, dose of lithium and the serum lithium levels, development of cutaneous side effects was collected. Patients were divided arbitrarily into 3 groups based on the dose of lithium - <800mg, 800-1200mg and > 1200mg. They were also divided into three groups according to serum lithium level as <0.8, 0.8-1.2, >1.2mEq/L and based on duration of lithium therapy - <6months, 6 months -1year and > 1 year.

History regarding skin lesion was obtained and physical examinations was done to check for the presence of skin lesions in sun light for all the patients, with the check list describing the skin lesions, after consulting with the dermatologist. . If the patient has any pre-existing skin lesions they were taken over to the dermatologist and necessary treatment were given for the lesions.

Follow ups:

After initial assessment all the patients were followed up periodically at 4^{th}, 8^{th}, 12^{th}, 16^{th}, 20^{th} and 24^{th} weeks. After that they were followed up for once in two months at 8^{th}, 10^{th} and 12^{th} months. At each follow up were assessed using follow up semi-structured proforma. It includes assessment of the dosage of lithium, serum lithium level, duration of lithium therapy and the development of new skin lesions. The change in the courses of pre-existing skin lesions was assessed. The change of lithium dose was assessed as reduced or maintained or change over to other mood stabilizers.

During each follow ups patients were asked for any skin lesions and physical examinations was done. If the patient develop any new skin lesions dermatologist opinion were sought each time and were give oral medications and topical applicants. The course of the skin lesions were assessed as static, worsened or improved.

If the patient missed a follow up they were contacted over phone and enquired for the presence of any skin lesions. If the patient has any skin lesions they were reinforced to come for follow up.

SAMPLE SIZE ESTIMATION:

We calculated sample size by using prevalence of skin lesion in previous study which is 3- 45%. By keeping prevalence as 45% we calculated sample size using the following formula.

$$N = 4PQ / d^2$$

P= Prevalence (From previous study)

Q= 100-P

d= Allowable error (5-20% of P)

Estimated sample size of our study is 177.We had recruited consecutive sample size within two and half month and followed up for 1 year.

STATISTICAL ANALYSIS:

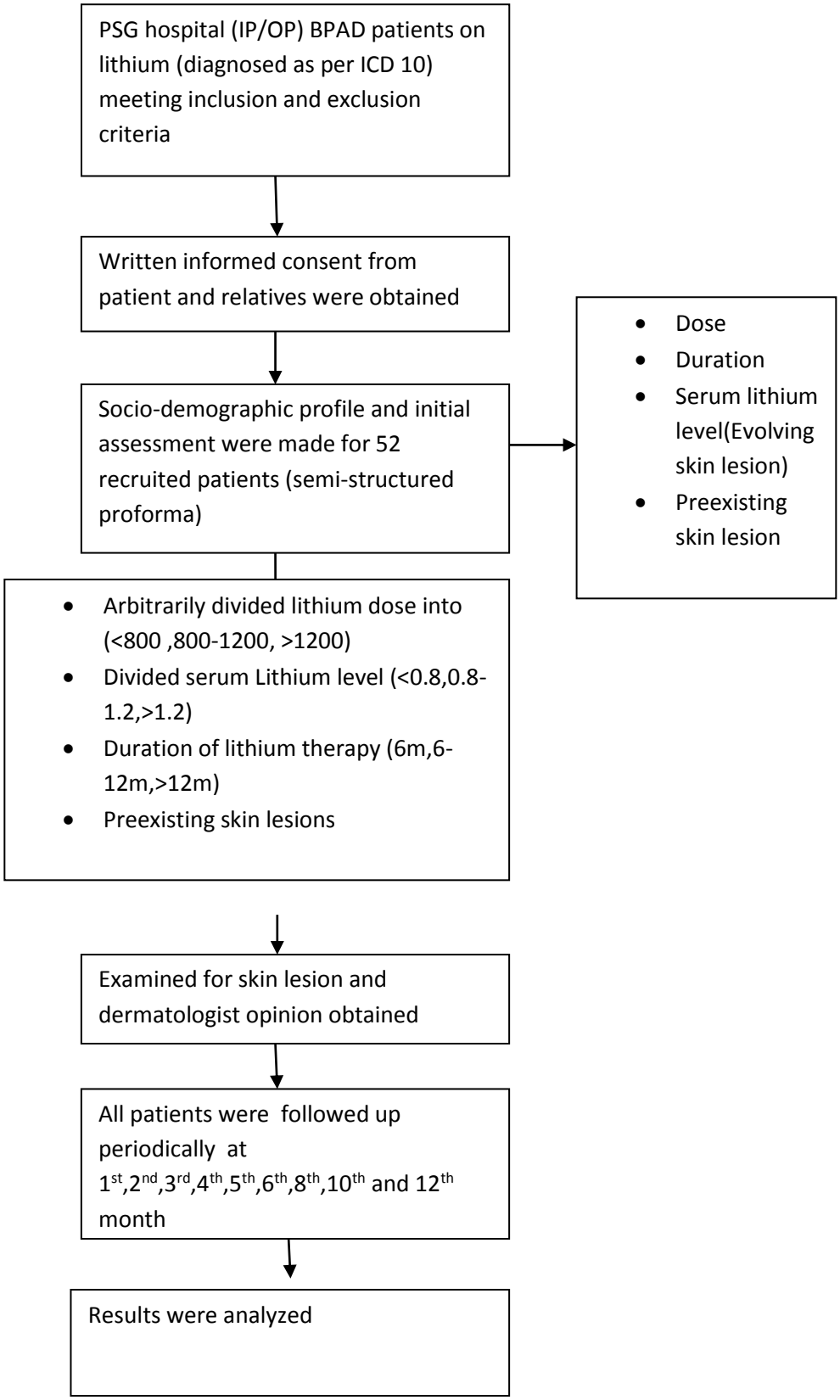
- Statistical analysis was conducted using soft ware package used for statistical analysis (SPSS) version 19.0 for windows.

- We compared the prevalence of skin reaction with the following variables such as Age, gender, Socio economic status and education and calculated using percentage.

- Mean standard deviation of lithium dose, serum lithium level and duration of lithium therapy was calculated and was expressed in bar diagram.
- Prevelance of skin lesions was calculated during percentage each follows up and was expressed in pie-chart diagram.

- Association of cutaneous lesion with dosage, serum lithium level in all follow ups was calculated using chi square test with statistical significance of $p<=0.05$.
- Association of cutaneous lesion with lithium dose, serum lithium level, and duration was done using independent student t-test.
- The course of pre-existing skin lesions was depicted graphical representation with x- axis denoting duration of follow up and y-axis denoting severity of illness.
- Prevalence of individual cutaneous leions are compared with the age, sex and socio-economic status and was calculated using percentage.

NO 1: FLOW CHART:



RESULTS:

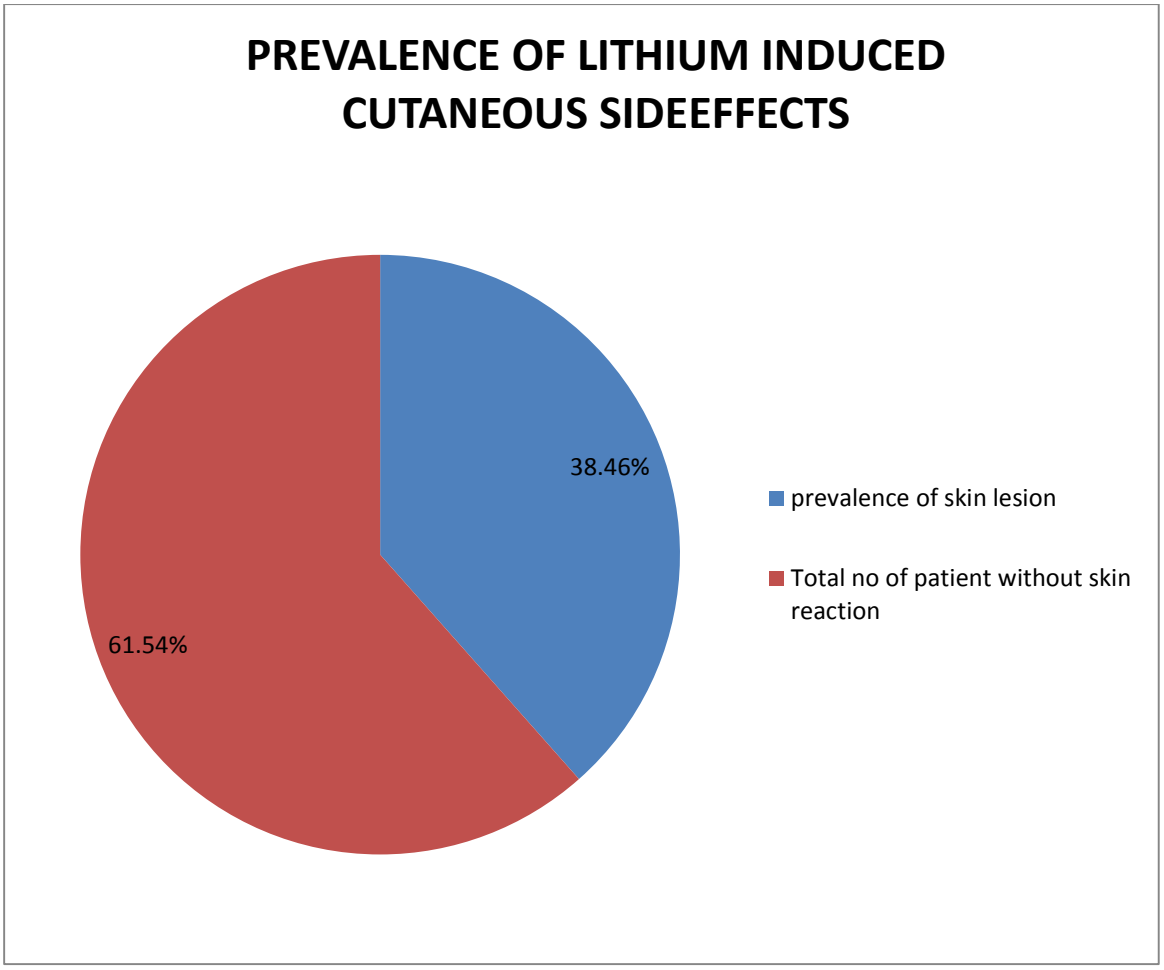
TABLE 1: BASELINE SOCIODEMOGRAPHIC DETAILS OF THE STUDY SAMPLE

VARIABLES	NUMBER OF PATIENTS (n)/ PERCENTAGE
Age in years	
< 40 years	31 (59.6%)
40-60years	18(34.6%)
>60years	3(5.8%)
Gender	
Female	25(48.1%)
Male	27(51.9%)
Socio-economic status	
Upper middle	49(94.2%)
Lower middle	3(5.8%)
Education	
Illiterate	15(28.8%)
Mid school	30(57.7%)
High school	7(13.5%)
Postgraduate	0

In the study sample 48.1% were females and 50.9% were males. The age groups were divided into less than 40years, 40-60 years and more than 60 years. 59.6% are less than 40 years, 34.6% are in the mid- adolescent age group and 5.8% are in the age group of more than 60 years.

Most of them had finished mid school level (6^{th}-10^{th} standard) of education (57.7%). 28.8% are illiterate and 13.5% are high school (10th-12^{th} standard).94.2% of the study sample were from upper middle SES and 5.8% from lower middle socio-economic status.

FIGURE 1:



Total prevalence of lithium induced skin reactions are **38.46%.**

DROPOUTS:

After recruitment of 52 patients, 10 were dropped out at the end of the study. Of which five were dropped out because of poor compliance. One dropped out within few days of recruitment as they developed lithium toxicity. One dropped out at the end of 3rd month due to persistent vomiting and he was changed over to another mood stabilizer. One dropped out at the end of 5th month as they are not affordable to do routine serum lithium level. Of the 10 drop outs, one had dropped out due to severe skin lesions due to lithium therapy. That case is a known case of systemic lupus erythematosis who had developed severe hairfall after starting lithium and they stopped lithium at the end of 3rd month.

CHART NO 2: DROPOUTS FLOW CHART:

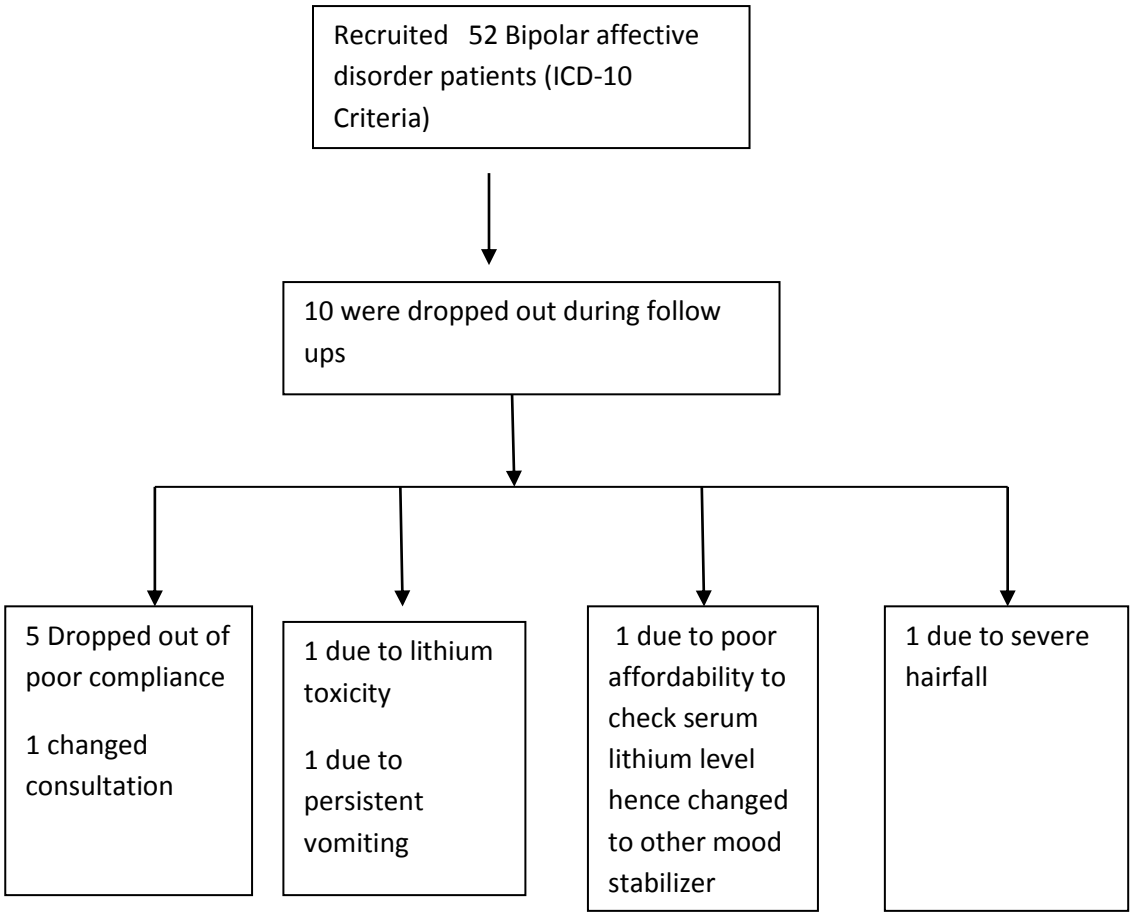


Table 2: Prevalence of skin lesions during first follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	10	19%
Hairfall	2	3.8%
Seborrheic dermatitis	1	1.9%
Acne & hyperpigmentation	1	1.9%
lithium induced ulcer	1	1.9%
Acne & hairfall	1	1.9%

During first follow up 10 had developed acneiform eruption, 2 had hairfall, 1 had combined acne and hyperpigmentation, and 1 had combined acne and hairfall, 1 had seborrheic dermatitis and 1 had lithium induced ulcers.

Table 3: Prevalence of skin lesions during second follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	11	20%
Hairfall	4	7.7%
Seborrheic dermatitis	1	1.9%
Acne, hyperpigmentation	1	1.9%
lithium induced ulcer	1	1.9%
Acne & hairfall	1	1.9%

During second follow up, 11 had developed acneiform eruption, 4 had hairfall, 1 had combined acne and hyperpigmentation, and 1 had combined acne and hairfall, 1 had seborrheic dermatitis and 1 had lithium induced ulcers

Table 4: Prevalence of skin lesions during third follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	10	19%
Hairfall	4	7.7%
Hyperpigmentation	1	1.9%
lithium induced ulcer	1	1.9%

During third follow up, 9 had developed acneiform eruption, 4 had hairfall, 1 had combined acne and hyperpigmentation, and 1 had hyperpigmentation and 1 had lithium induced ulcers.

Table 5: Prevalence of skin lesions during fourth follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	7	13.3%
Hairfall	6	11.4%
Hyperpigmentation	1	1.9%
lithium induced ulcer	1	1.9%
Acne & hairfall	1	1.9%

During fourth follow up, 7 had developed acneiform eruption, 6 had hairfall, 1 had combined acne and seborrheic dermatitis, and 1 had hyperpigmentation and 1 had lithium induced ulcers.

Table 6: Prevalence of skin lesions during fifth follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	4	7.6%
Hairfall	5	9.5%
Hyperpigmentation	2	3.8%
lithium induced ulcer	1	1.9%
Acne & hairfall	1	1.9%

During fifth follow up, 4 had developed acneiform eruption, 5 had hairfall, 1 had combined acne and seborrheic dermatitis, and 2 had hyperpigmentation and 1 had lithium induced ulcers.

Table 7: Prevalence of skin lesions during sixth follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	6	11.5%
Hairfall	4	7.7%
Hyperpigmentation	2	3.8%
lithium induced ulcer	1	1.9%

During sixth follow up, 6 had developed acneiform eruption, 4 had hairfall, and 2 had hyperpigmentation and 1 had lithium induced ulcers.

Table 8: Prevalence of skin lesions during seventh follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	5	11.5%
Hairfall	4	7.7%
Seborrheic dermatitis	1	1.9%
Hyperpigmentation	2	3.8%
lithium induced ulcer	1	1.9%
Acne & seborrheic dermatitis	1	1.9%

During seventh follow up, 5 had developed acneiform eruption, 4 had hairfall, and 2 had hyperpigmentation, 1 had lithium induced ulcers, 1 had combined lithium with seborheic dermatitis and 1 had seborrheic dermatitis.

Table 9: Prevalence of skin lesions during eight follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	3	5.8%
Hairfall	4	7.7%
Seborrheic dermatitis	1	1.9%
Hyperpigmentation	2	3.8%
lithium induced ulcer	1	1.9%
Acne & seborrheic dermatitis	1	1.9%

During eighth follow up, 3 had developed acneiform eruption, 4 had hairfall, and 2 had hyperpigmentation, 1 had lithium induced ulcers, 1 had combined lithium with seborheic dermatitis and 1 had seborrheic dermatitis.

Table 10: Prevalence of skin lesions during ninth follow up:

Skin lesion	Frequency (n)	Percentage %
Acneiform eruption	1	1.9%
Hairfall	7	13.3%
Seborrheic dermatitis	1	1.9%
Hyperpigmentation	2	3.8%
lithium induced ulcer	1	1.9%
Acne & seborrheic dermatitis	1	1.9%

During eighth follow up, 1 had developed acneiform eruption, 7 had hairfall, and 2 had hyperpigmentation, 1 had lithium induced ulcers, 1 had combined lithium with seborheic dermatitis and 1 had seborrheic dermatitis.

TABLE 11: PREVALENCE OF CUMULATIVE SUBTYPE OF SKIN LESIONS:

S.NO	Type of skin lesion	Initial	F1	F2	F3	F4	F5	F6
1	Acneiform eruption	7(13.3%)	10(19%)	11(20%)	9(17.3%)	7(13.3%)	4(7.6%)	6(11.5%)
2	Hairfall	1(1.9%)	2(3.8%)	4(7.7%)	4(7.7%)	6(11.4%)	5(9.5%)	4(7.7%)
3	Seborrheic dermatitis	0	1(1.9%)	1(1.9%)	0	0	0	0
4	Hyperpigmentation	0	0	0	1(1.9%)	1(1.9%)	2(3.8%)	2(3.8%)
5	Acne & Hyperpigmentation	1(1.9%)	1 (1.9%)	1 (1.9%)	1(1.9%)	0	0	0
6	Lithium induced ulcer	0	1(1.9%)	1(1.9%)	1(1.9)	1(1.9%)	1(1.9%)	1(1.9%)
7	Acne & Hairfall	0	1(1.9%)	1(1.9%)	0	0	0	0
8	Acne & seborrheic dermatitis	0	0	0	0	1(1.9%)	1(1.9%)	0

Baseline prevalence of cumulative subtype of skin lesions:

During initial recruitment 9 patients had developed skin lesions. During initial assessment 7 had developed acneiform eruptions, 1 had developed hairfall and 1 had combined type acneiform eruptions and hyperpigmention.

TABLE 12: PREVALENCE OF CUMULATIVE SUBTYPE OF SKIN LESIONS:

S.NO	Type of skin lesion	F7	F8	F9
1	Acneiform eruption	5(9.6%)	3(5.8)	1 (1.9%)
2	Hairfall	4(7.7%)	4(7.7%)	7(13.3%)
3	Seborrheic dermatitis	1(1.9%)	1(1.9%)	1(1.9%)
4	Hyperpigmentation	2 (3.8%)	2 (3.8%)	2 (3.8%)
5	Acne & Hyperpigmentation	0	0	0
6	Lithium induced ulcer	1(1.9%)	1(1.9%)	1(1.9%)
7	Acne & Hairfall	0	0	0
8	Acne & seborrheic dermatitis	1(1.9%)	1(1.9%)	1(1.9%)

ANALYSIS OFCUMULATIVE PREVALENCE OF SKIN LESIONS DURING 1 YEAR FOLLOW UP:

We have looked for the prevalence of individual skin lesion and its outcome with treatment during 1 year follow-up.

- An Acneiform eruption has increased from baseline to 2nd and 3rd follow up and has gradually reduced at the end of 1 year from 19% to 1.9%.
- Hairfall has increased from baseline to the end of 1 year from 1.9% to 7.7%.
- 1.9% has developed seborrheic dermatitis at 2nd and 3rd follow up which has cleared at the end of 6th follow up and again reoccurred at the end of 1 year in 1.9%.
- Hyperpigmentation has developed during 3rd follow up and has increased at the end of 1 year from 1.9% to 3.8%
- Combined acne with hyperpigmentation has developed in 1.9% from baseline to 3rd follow up and has cleared during further follow ups.
- Lithium induced ulcer has developed in 1st follow up and persisted throughout. It has developed in the right index and middle fingers with multiple ulcers gradually it has increased its size and number of ulcers during each follow up. But after the end of the study, lithium was stopped and was changed over to other mood stabilizers.
- Combined acneiform eruptions and hairfall has occurred in 1.9% during 1st and 2nd follow up and thereafter cleared at the end of the study.
- Combined acneiform eruption and seborrheic dermatitis has occurred in 1.9% in the4th and 5th follow up and cleared at the end of the study.

TABLE 13: PREVALENCE OF LITHIUM INDUCED SKIN REACTION AMONG VARIOUS DOSES OF LITHIUM:

FOLLOW UP	<800 mg		800-1200 mg		➢ 1200 mg		X^2
Initial	2/20	10%	8/26	30.8%	2/6	33.3%	0.207
Follow up 1	1/14	7.1%	4/27	14.8%	3/8	37.5%	0.171
Follow up 2	1/12	8.3%	4/27	14.8%	3/8	37.5%	0.338
Follow up 3	2/10	20.0%	5/26	19.2%	4/9	44.4%	0.156
Follow up 4	1/7	14.3%	4/25	16%	3/8	37.5%	0.530
Follow up 5	1/7	14.3%	5/24	20.8%	1/7	14.3%	0.923
Follow up 6	1/7	14.3%	6/23	26.1%	1/7	14.3%	0.801
Follow up 7	1/7	14.3%	6/22	27.3%	2/8	25%	0.845
Follow up8	2/16	12.5%	3/17	17.6%	2/4	50%	0.353
Follow up 9	1/7	14.3%	3/22	13.6%	1/8	12.5%	0.983

Prevalence of lithium induced skin lesions is not statistically significant comparing with varying dose.

FIGURE 2: COMPARISON OF SKIN LESIONS BETWEEN THREE GROUPS OF DOSES

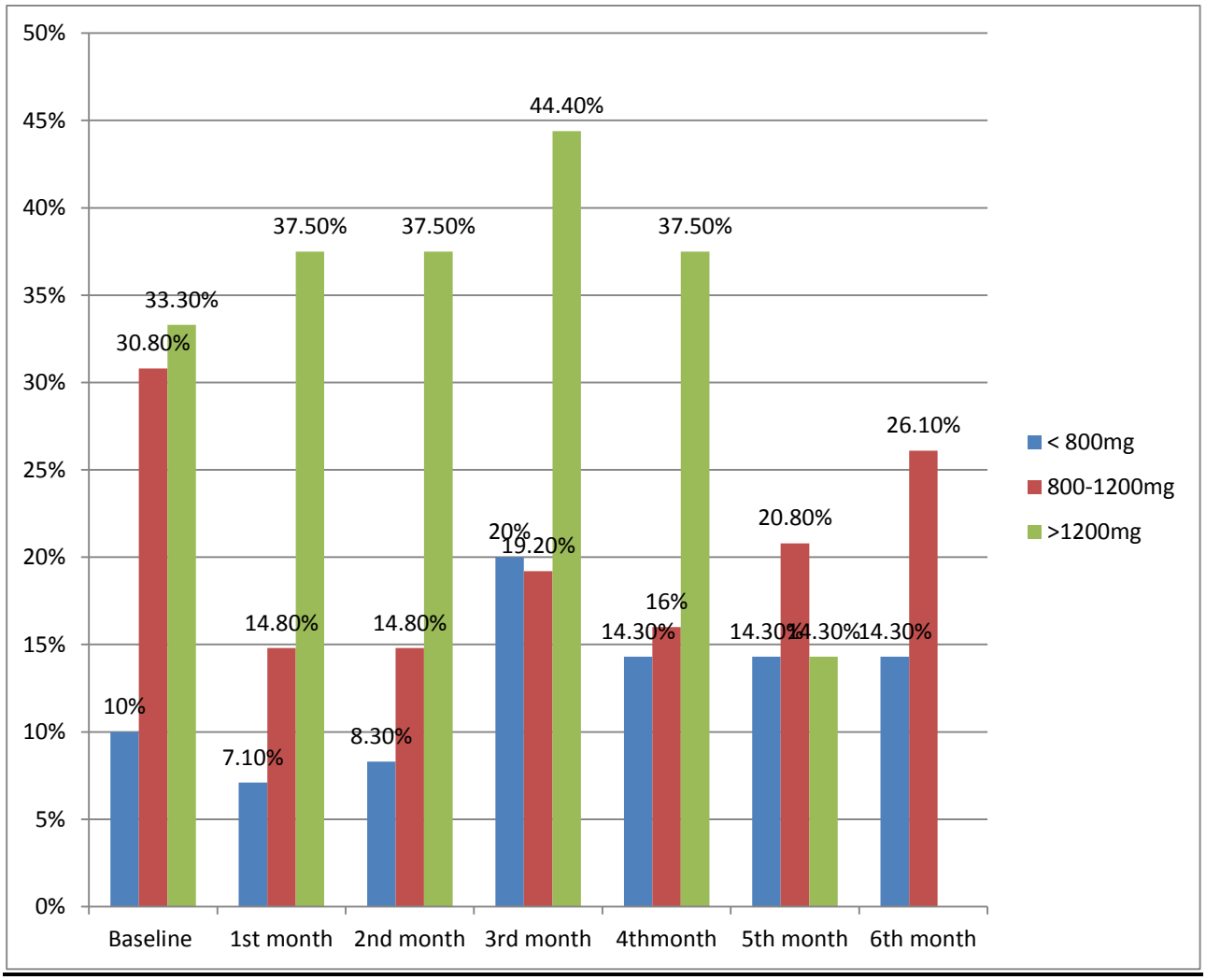


FIGURE 3: COMPARISON OF SKIN LESIONS BETWEEN THREE GROUPS OF DOSES DURING LAST THREE FOLLOW UPS:

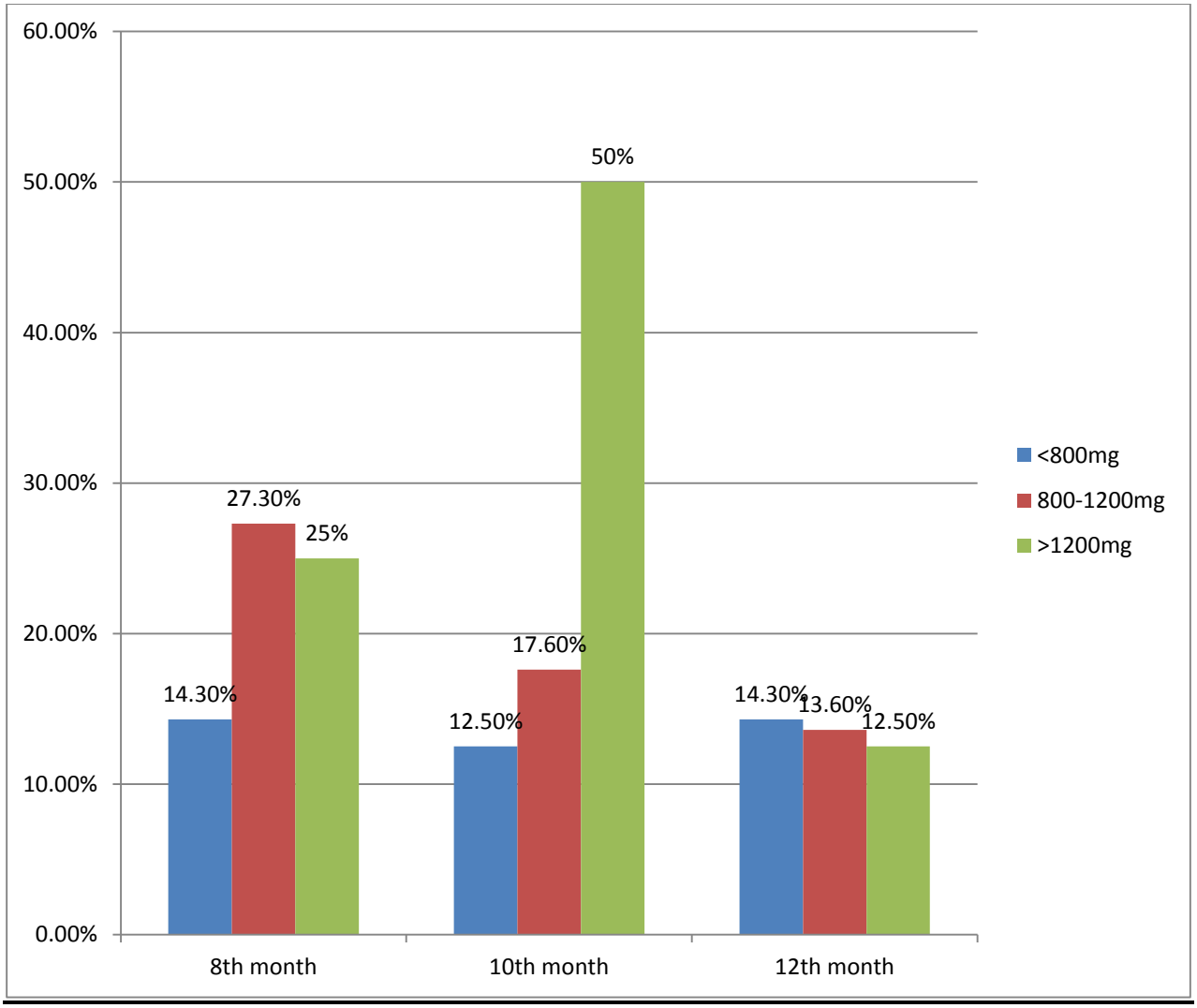


TABLE 14: PREVALENCE OF LITHIUM INDUCED SKIN REACTION AMONG VARIOUS SERUM LITHUM LEVELS:

Follow ups	**<0.8 meq/L**		**0.8-1.2 meq/L**		**> 1.2 meq/L**		**X^2**
Initial	3/25	12.0%	8/20	40.8%	1/7	14.3%	0.072
Follow up 1	2/21	9.5%	5/23	21.7%	1/5	20%	0.534
Follow up2	2/20	10%	6/23	26.1%	0/5	0%	0.211
Follow up 3	4/19	21.1%	6/22	27.3%	2/5	40%	0.681
Follow up 4	1/16	6.3%	6/20	30%	1/4	25%	0.319
Follow up5	1/15	6.7%	4/19	21.1%	2/4	50%	0.219
Follow up 6	2/15	13.3%	3/17	17.6%	3/5	60%	0.139
Follow up 7	3/16	18.8%	3/17	17.6%	3/4	75%	0.082
Follow up 8	2/16	12.5%	3/17	17.6%	2/4	50%	0.353
Follow up 9	1/16	6.3%	3/17	17.6%	1/4	25%	0.657

Prevalence of lithium induced skin lesions is not statistically significant comparing with varying serum lithium level

FIGURE 4: COMPARISON OF SKIN LESIONS BETWEEN THREE GROUPS OF SERUM LITHIUM LEVEL

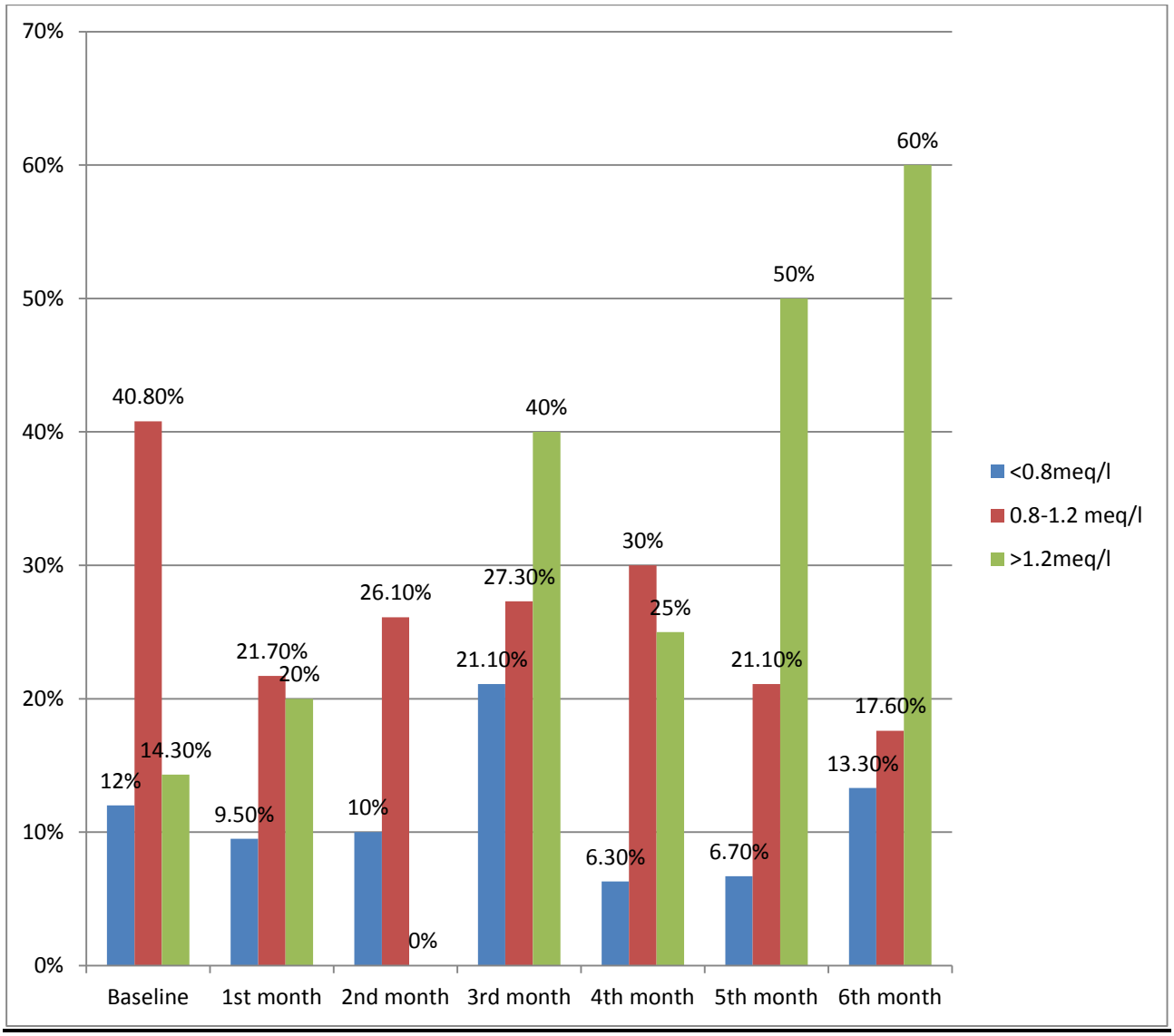


FIGURE 5: COMPARISON OF SKIN LESIONS BETWEEN THREE GROUPS OF SERUM LITHIUM LEVEL DURING LAST THREE FOLLOW UPS

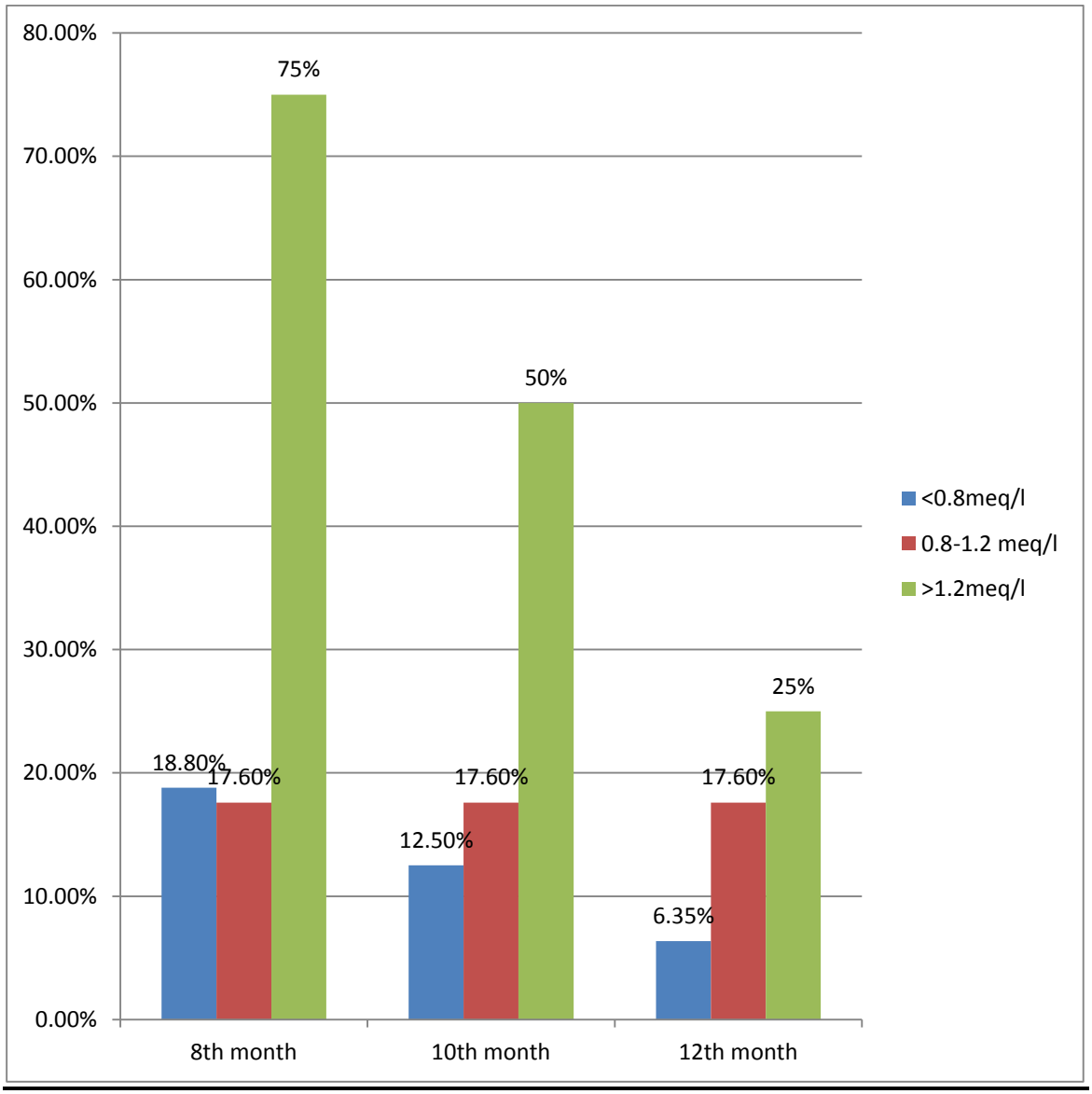


TABLE 15: PREVALENCE OF LITHIUM INDUCED SKIN REACTION AMONG VARIOUS DURATION OF LITHUM LEVELS:

Follow up	<6 months		6months-1 year		>1 year		X^2
Initial	3/16	18.8%	1/5	20%	8/31	25.8%	0.850
Follow up 1	3/15	28.6%	1/4	25%	4/30	13.3%	0.754
Follow up 2	4/14	28.6%	1/5	20%	3/29	10.3%	0.316
Follow up 3	4/13	30.8%	3/4	75%	5/29	17.2%	**0.043**
Follow up 4	5/14	35.7%	0/1	0%	3/25	12%	0.293
Follow up 5	2/12	16.7%	0/1	0%	5/25	20.0%	0.914
Follow up 6	3/11	27.3%	0/1	0%	5/25	20%	0.848
Follow up 7	3/11	27.3%	0/1	0%	6/25	24%	0.873
Follow up 8	3/11	27.3%	0/1	0%	4/25	16%	0.772
Follow up 9	2/11	18.2%	0/1	0%	3/25	12%	0.902

Prevalence of lithium induced skin lesions is statistically significant during third follow up as (P value <0.043) .

No significance has noticed in all other follow ups comparing with varying duration of lithium therapy.

FIGURE 6: COMPARISON OF SKIN LESIONS BETWEEN THREE GROUPS OF DURATION OF LITHIUM THERAPY

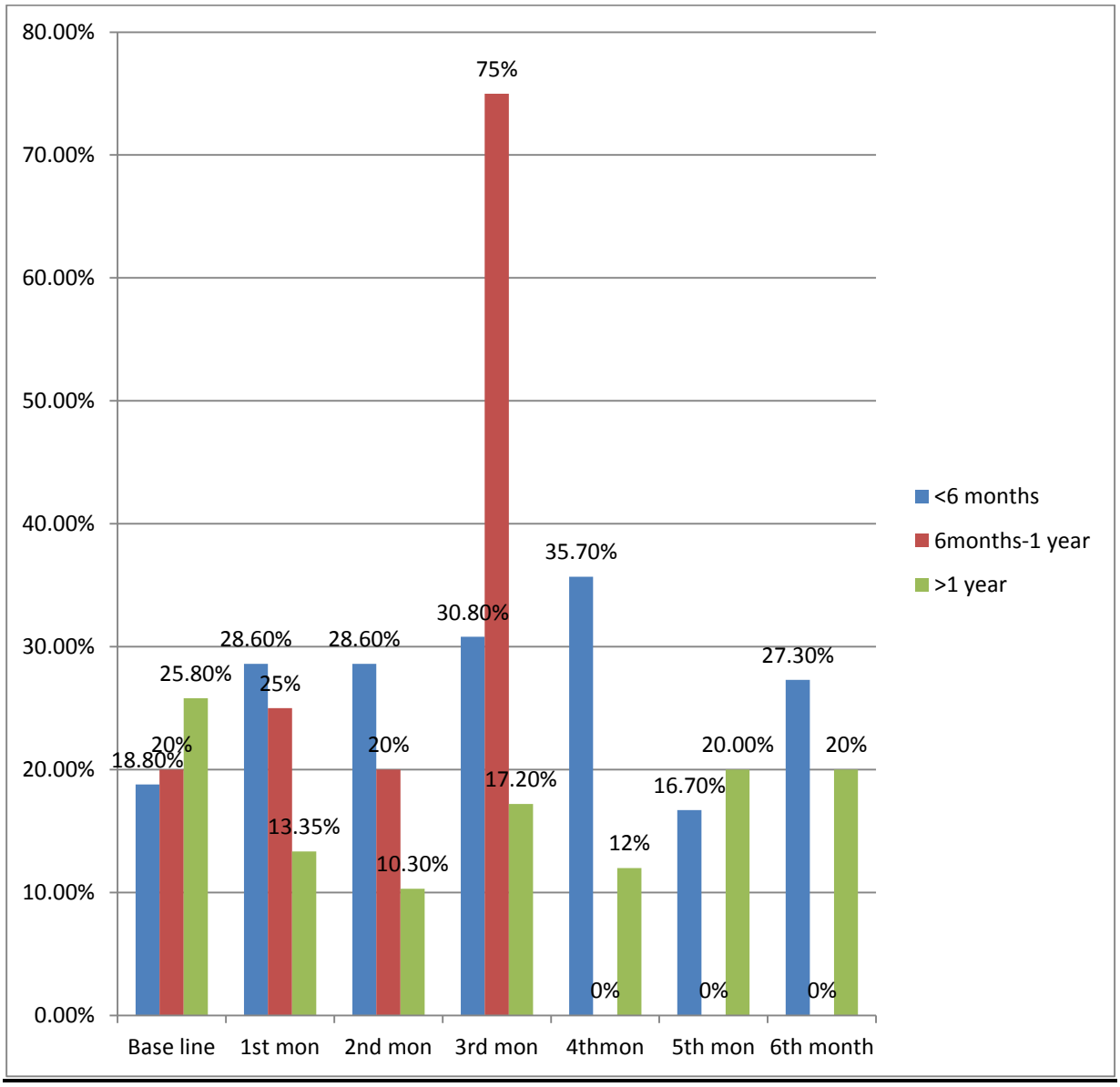


FIGURE 7: COMPARISON OF SKIN LESIONS BETWEEN THREE GROUPS OF DURATION OF LITHIUM THERAPY DURING LAST THREE FOLLOW UPS

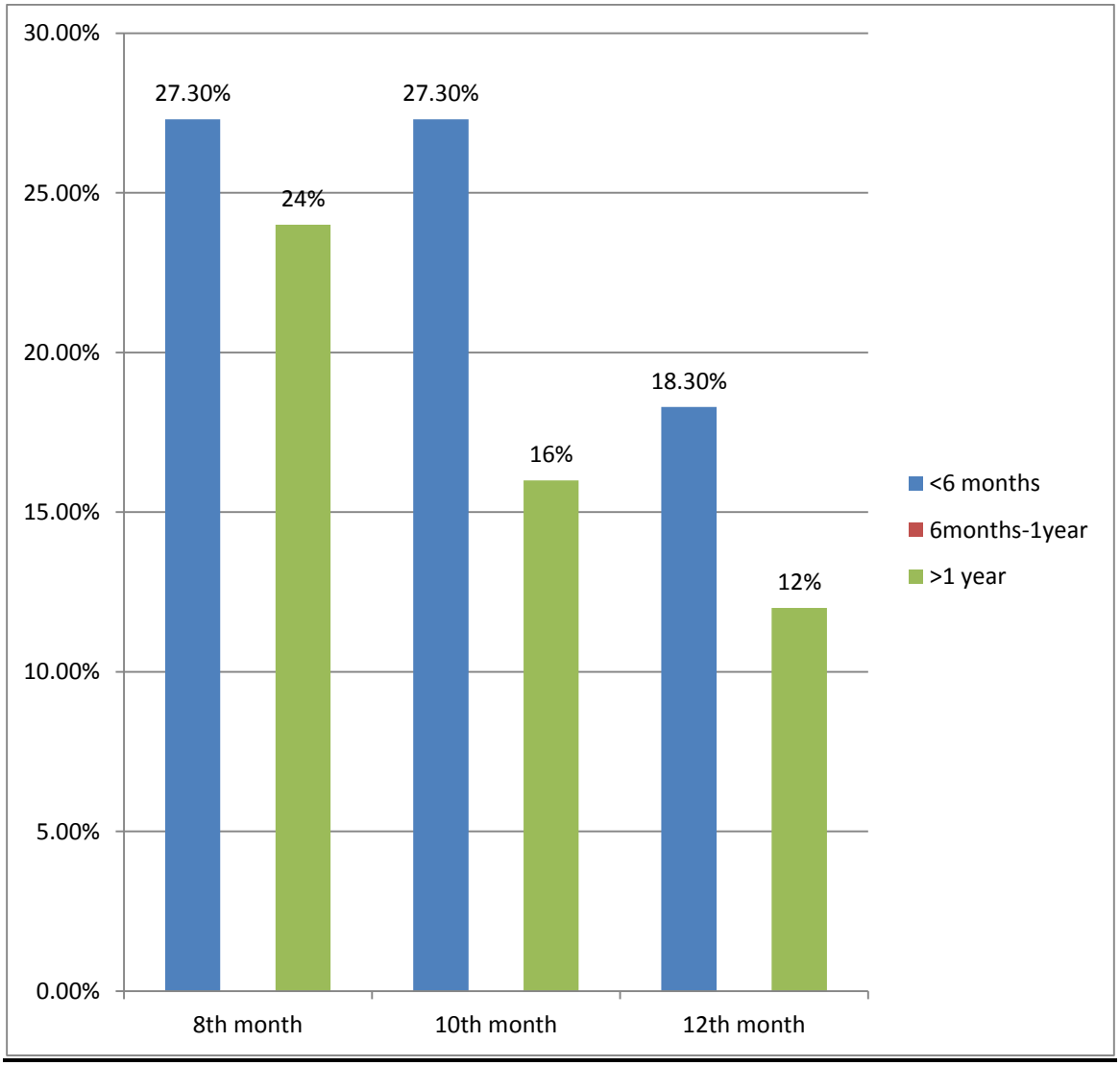


TABLE 16: MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 1ST MONTH:

Follow up 1	Mean value	Standard deviation
Dose of lithium	1150	297
Serum lithium level	0.94	0.19
Duration of lithium therapy	15.2	13

Mean value of lithium dose, serum lithium level and duration calculated during 1st month.

TABLE 17: MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 2nd MONTH:

Follow up 2	Mean value	Standard deviation
Dose of lithium	1125	319
Serum lithium level	0.9	0.15
Duration of lithium therapy	11.75	10.49

Mean value of lithium dose, serum lithium level and duration calculated during 2nd month.

TABLE 18:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 3rd MONTH:

Follow up 3	Mean value	Standard deviation
Dose of lithium	1050	320.5
Serum lithium level	0.92	0.138
Duration of lithium therapy	16.6	15.2

Mean value of lithium dose, serum lithium level and duration calculated during 3rd month.

TABLE 19:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 4rd MONTH:

Follow up 4	Mean value	Standard deviation
Dose of lithium	975	249.2
Serum lithium level	0.91	0.14
Duration of lithium therapy	18.50	21.4

Mean value of lithium dose, serum lithium level and duration calculated during 4th month.

TABLE 20:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 5th MONTH:

Follow up 5	Mean value	Standard deviation
Dose of lithium	971	314.7
Serum lithium level	0.86	0.13
Duration of lithium therapy	36.7	41.2

Mean value of lithium dose, serum lithium level and duration calculated during 5th month.

TABLE 21:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 6th MONTH:

Follow up 6	Mean value	Standard deviation
Dose of lithium	1000	302.3
Serum lithium level	0.85	0.12
Duration of lithium therapy	33.7	39.7

Mean value of lithium dose, serum lithium level and duration calculated during 6th month.

TABLE 22:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 8th MONTH:

Follow up 7	Mean value	Standard deviation
Dose of lithium	1000	282.8
Serum lithium level	0.86	0.12
Duration of lithium therapy	33.5	37.7

Mean value of lithium dose, serum lithium level and duration calculated during 8th month.

TABLE 23:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 10th MONTH:

Follow up 8	Mean value	Standard deviation
Dose of lithium	1028	269
Serum lithium level	0.87	0.13
Duration of lithium therapy	35.14	43.32

Mean value of lithium dose, serum lithium level and duration calculated during 10th month.

TABLE 24:MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION DURING 12th MONTH:

Follow up 9	Mean value	Standard deviation
Dose of lithium	1000	316.2
Serum lithium level	0.87	0.16
Duration of lithium therapy	45.6	49.9

Mean value of lithium dose, serum lithium level and duration calculated during 12th month.

TABLE 25: MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION:

Follow ups	**Skin lesion**	**Lithium characteristics**	**Significance**
Follow up 1	Present: 8 Absent: 41	Mean dose:1150 (297) Mean SLL: 0.94(0.13) Mean duration: 15.25(0.19)	P=0.507 P=0.601 **P=0.016**
Follow up 2	Present :8 Absent: 40	Mean dose:1125 (319.5) Mean SLL: 0.93(0.15) Mean duration:11.7(10.4)	P=0.933 P=0.238 **P=0.011**
Follow up 3	Present :12 Absent: 34	Mean dose: 1050(320.5) Mean SLL: 0.92(0.13) Mean duration: 16.6(15.2%)	P=0.895 P=0.105 **P=0.005**
Follow up 4	Present: 8 Absent: 33	Mean dose: 975(249.2) Mean SLL: 0.91(0.14) Mean duration:18.5(21.4)	P=0.226 P=0.16 P=0.06

TABLE 26: MEAN LITHIUM DOSE, DURATION AND SERUM LITHIUM LEVEL WITH LITHIUM INDUCED SKIN REACTION:

Follow up	Skin lesion	Lithium characteristics	Significance
Follow up 5	Present: 7 Absent: 32	Mean dose: 971(314.7) Mean SLL: 0.8(0.13) Mean duration:36.7(41.2)	P=0.85 P=0.20 P=0.46
Follow up 6	Present: 8 Absent:30	Mean dose: 1000(302.3) Mean SLL: 0.85(0.12) Mean duration:33.7(37.7)	P=0.71 P=0.115 P=0.404
Follow up 7	Present: 9 Absent:29	Mean dose: 1000(282.8) Mean SLL: 0.86(0.12) Mean duration:33(37.7)	P=0.434 P=0.068 P=0.315
Follow up 8	Present: 7 Absent:31	Mean dose: 1028(269.0) Mean SLL: 0.87(0.139) Mean duration: 35.1 (43.3)	P=0.369 P=0.200 P=0.636
Follow up 9	Present: 5 Absent:33	Mean dose: 1000(316.2) Mean SLL: 0.87 (0.16) Mean duration: 5(45.6)	P=0.723 P=0.447 P=0.982

ANALYSIS OF CLINICAL PARAMETERS OF LITHIUM (DOSAGE, DURATION,SERUM LITHIUM LEVELS) WITH SKIN LESIONS:

Prevalence of course of lithium induced cutaneous reactions were compared with the dose,serum lithium level and durations during each follow ups and are not statistically significant.

So we consider taking the mean value of lithium dose, serum lithium level and duration and compared with the presence or absence of skin reaction during each follow up.

The mean values of duration of lithium therapy are statistically significant during the 1st, 2nd and 3rd follow up with 15, 11 and 16 month of duration of lithium.

Hence patients who were on the longer the duration of lithium therapy (> 11months) were prone for lithium induced cutaneous side effects.

TABLE 27: PERCENTAGE OF CUTANEOUS LESIONS IN VARIOUS AGE GROUPS:

Age	Acneiform Eruption	Hairfall	Seborrheic dermatitis	Hyperpigmentation	Lithium induced ulcer
Early adulthood	11 (20%)	3 (5.7%)	1 (1.9%)	2 (3.8%)	0
Late adulthood	2 (3.8%)	3 (5.7%)	0	1 (1.9%)	1 (1.9%)
Geriatrics	1 (1.9%)	0	0	1 (1.9%)	0

Acneiform eruptions (20%) and hyperpigmentation (3.8%) are more common in early adulthood, where as lithium an induced ulcer has seen in late adulthood. Hairfall is equal in both early and late adulthood around 5.7%.

TABLE 28: PERCENTAGE OF CUTANEOUS LESIONS IN VARIOUS AGE GROUPS:

Age	Acne, hyperpigmentation	Acne, Hairfall	Acne, Seborrheic dermatitis
Early adulthood	0	1 (1.9%)	1 (1.9%)
Late adulthood	0	1 (1.9%)	0
Geriatrics	1 (1.9%)	0	0

1.9% of acneiform eruptions with hyperpigmentation occurred in geriatric age group, acne with hairfall (1.9%) occurred in early adulthood and Lithium with seborrheic dermatitis (1.9%) occurred in early adulthood.

TABLE 29: GENDER DIFFERENCES IN PREVALENCE OF CUTANEOUS SKIN LESIONS:

Age	Acneiform Eruption	Hairfall	Seborrheic dermatitis	Hyperpigmentation	Lithium induced ulcer
Female	6 (11.4%)	4 (7.6%)	0	1 (1.9%)	1 (1.9%)
Male	8 (15.2%)	2 (3.8%)	1 (1.9%)	2 (3.8%)	0

- 15.2% Acneiform eruptions occurred in male and 11.4% occurred in females.
- 7.6% hairfall occurred in females and 3.8% in males
- 1.9% case of seborrheic dermatitis occurred in males.
- 3.8% males had developed hyperpigmentation and 1.9% developed in females.
- 1.9% female had developed lithium induced ulcers.

TABLE 30: GENDER DIFFERENCES IN PREVALENCE OF CUTANEOUS SKIN LESIONS:

Sex	Acneiform Hyperpigmentation	Acneiform, Hairfall	Acneiform, Seborrheic dermatitis
Female	0	2 (3.8%)	0
Male	2 (3.8%)	0	1 (1.9%)

3.8% females had developed acneiform with hairfall where as acneiform eruption with hyperpigmentation (3.8%) and seborrheic dermatitis (1.9%) occurred in males.

TABLE 31: PERCENTAGE OF CUTANEOUS LESIONS AMONG MIDDLE SOCIO-ECONOMIC STATUS:

SES	Acneiform Eruption	Hairfall	Seborrheic dermatitis	Hyperpigmentation	Lithium induced ulcer
Upper middle	12 (22.8%)	3 (5.7%)	1 (1.9%)	2 (3.8%)	0
Lower Middle	1 (1.9%)	1 (1.9%)	0	0	1 (1.9%)

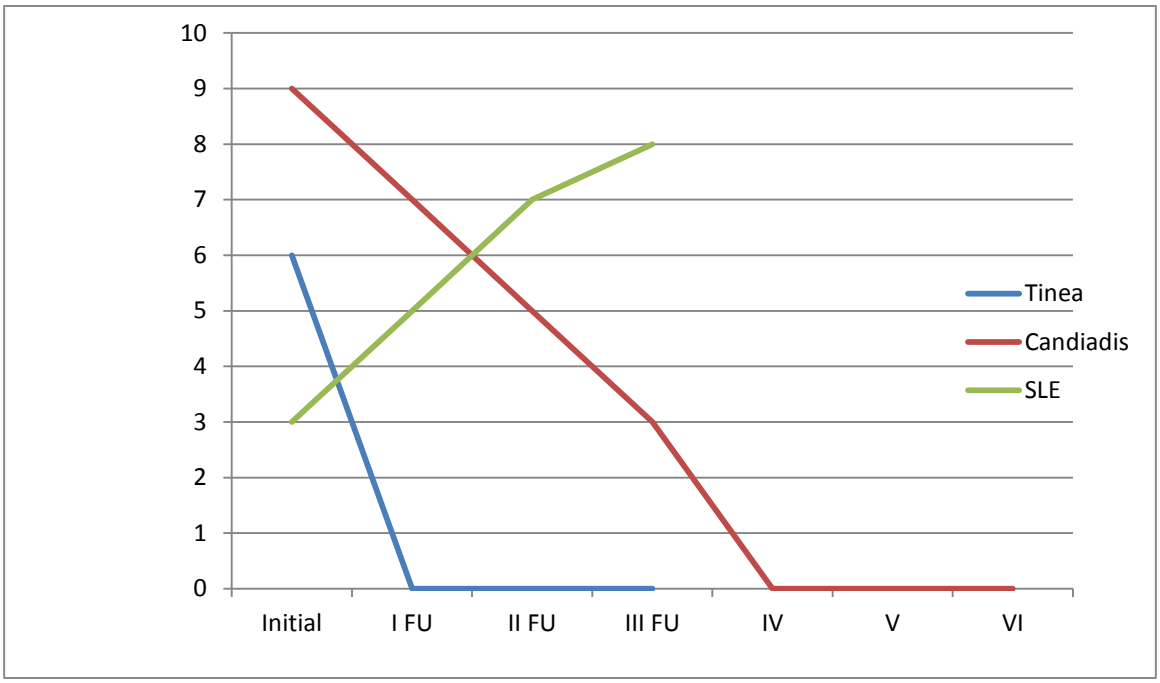
Most of the lesions occurred in upper middle socio-economic status. 22.8% of acneiform eruptions, 5.7% of hairfall, 1.9% of seborrheic dermatitis and 3.8% of hperpigmentations occurred in upper middle socio-economic status**.**1.9% of acneiform eruptions, hairfall and lithium induced ulcers occurred in lower middle socio-economic status.

TABLE 32: PERCENTAGE OF CUTANEOUS LESIONS IN VARIOUS SOCIO-ECONOMIC STATUS:

Age	Acne, hyperpigmentation	Acne, Hairfall	Acne, Seborrheic dermatitis
Upper middle	1 (1.9%)	1 (1.9%)	1 (1.9%)

1.9% of acneiform eruptions co-exist with hyperpigmentation ,hairfall and seborrheic dermatitis occured in upper-middle socio economic status.

FIGURE 8: Course of pre-existing skin lesions:



- Tinea during recruitment has gradually subsided with treatment during 3rd month
- SLE has developed severe hairfall at 2nd month and dropped out from the study during 3rd month.
- Candidiasis has gradually improved and remitted during 4th month

DISCUSSION

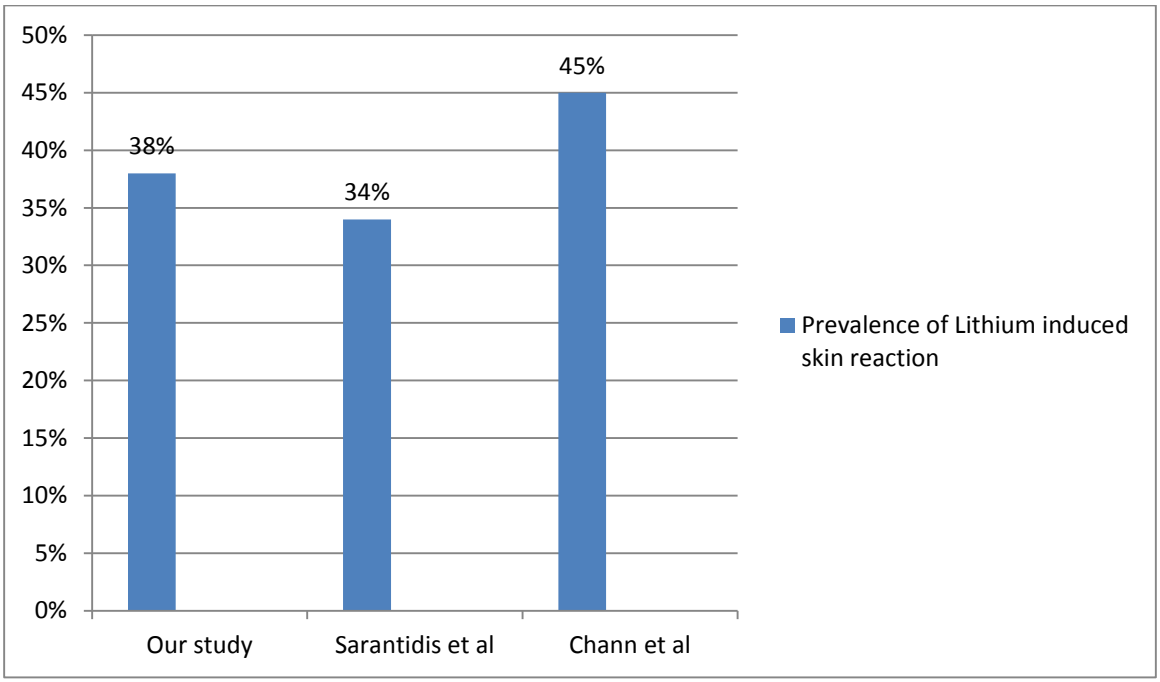
Our prospective observational study was designed to find the prevalence of cutaneous side effects in bipolar affective disorder patients on lithium therapy. We looked for the relationship between the dose, serum lithium level and duration of lithium therapy and the cutaneous side effects.

To start with, we recruited bipolar affective disorder patients who fulfilled the ICD-10 criteria, and who were on lithium. The mean age of our sample was 38.6 years and most common age group was early adulthood (18-40 years). Our sample had an equal gender distribution. Most were in the upper middle socio-economic status and had completed up to middle school 3education.

In our study the dropout rate was 19% . One patient dropped out because of systemic side effect and 1 more due to lithium toxicity. One patient with pre-existing systemic lupus erythematosis dropped out due to severe hair fall. Patients with poor compliance and who were not able to afford lithium level monitoring and hence were changed to other mood stabilizers by the primary therapist were also considered as having dropped out.

On analyzing the prevalence of lithium induced skin reactions in our study was **38.46%** which is comparable to the prevalence reported by Sarantidis et al and Chann et al.

FIGURE 33: COMPARING OUR PREVALENCE WITH OTHER STUDY



Acneiform eruption and hairfall were the most common side effects on assessing the prevalence of skin reaction during each follow ups. In the initial 2 months acneiform eruptions was more common than hairfall but during the later months (6th, 8th and 9th month) hairfall was found to have a higher prevalence.

On assessing the cumulative subtype of skin reactions, **Incidence of hyperpigmentation** was noticed to be significantly higher in our study compared to previous studies. Acneiform eruptions and hair fall are most common lesion in our study whereas study by Sarantidis at al showed acneiform eruption and psoriasis as the most common secondary cutaneous lesions.

The Course of acneiform eruption showed that the lesions were more during initial follow up and gradually improved on treatment with topical retinoids. The patients who developed this had the classical type of distribution over the extremities (mostly in the back of the shoulders) as reported in previous studies by Jennis and Kerbs et al.

Hyperpigmentation, hairfall and seborrheic dermatitis **co-exist** with acneiform eruptions during the course. Seborrheic dermatitis has reduced along the course with treatment but reappears on discontinuation of treatment for the same but when compared with previous study by Dreno et al where lithium is used as the treatment for seborrheic dermatitis. Co-existing skin reactions are not discussed in previous study.

In our study one patient had developed lithium induced ulcers. She had multiple small pustular ulcers over the index and middle fingers which was found to be most distressing for the patient. Even with treatment with topical applications patient continued to have repeated pustular ulcers in hands with fissure.

Our study has shown different dosage don't correlate statistically with lithium induced cutaneous side effects. The different levels of serum lithium don't statistically correlate with lithium induced skin reaction.

In our study mean duration of the lithium treatment was (11 – 15 months duration) which was statistically significant and has shown that longer the duration more is the occurrence of cutaneous side effects. But in previous study by sarantidis et al, Chann et al no significant association was noticed. .

The cutaneous adverse reactions on lithium are more common in early adulthood than in the late adulthood and geriatric age group and among the subtypes of skin lesion acneiform eruptions are more common among males than in females which is supported by previous study by Chan et al. Acneiform eruptions coexists with hairfall and is more common among females. An acneiform eruption with hyperpigmentation is more common among males. All cutaneous lesions occur in upper-middle socio-economic status while lithium induced ulcer occurred in lower-middle socio-economic status.

Patient with pre-existing severe skin reactions are prone for new skin reaction and may contribute to poor attrition. Interestingly, patients with milder skin reactions like tinea and candidiasis improved over the course of time.

Neither stoppage nor dose reduction was done in the patients who had developed skin reactions. They were also not changed over to other mood stabilizer.

STRENGTH:

Our study is the prospective study; we had recruited the patient and followed them up for 1 year prospectively which is the strength of our study than in previous study they had cross sectional compared the patient on lithium and other psychotropic medication.

We had assessed the relationship between the doses, duration and serum lithium level with the cutaneous adverse effects which is the credential of the study.

We obtained qualified dermatologist opinion for each patient with lithium induced cutaneous side effects.

Each patient were seen and assessed on nine occasions and they were encouraged to come for follow up if they missed.

LIMITATION;

Our sample size was 52 which is small to be generalized

We followed up only for shorter duration of 12 months; a longer follow up would be more credential.

We had also included few patients on lithium along with psychotropic medications which would also contribute to the cutaneous lesions.

A single dermatologist assessing all the cohorts would have made the study better and it was not possible due to practical reasons.

Niranjo scale which is used to assess the association between the drug induced reaction and drug are not used in our study.

No blinding was done for the primary therapist nor for the dermatologist.

We followed the patients through telephonic calls which may not be correct as direct observation.

We were unable to alter the dose of lithium or to do a serum lithium level as it was at the discretion of the primary therapist.

Since none of the patient was stopped lithium we were unable to assess the course of skin lesion after stopping lithium.

CONCLUSION

Prevalence of Lithium induced cutaneous lesions continuous to be high. Clinician should educate the patient before initiating lithium to improve the attrition rate.

Prevalence doesn't vary between the dosage and the serum lithium level. Hence, Clinician need not be ambivalent about reducing the dose.

Prevalence increases with the duration of lithium treatment, which remitted with treatment. Hence therapist should be cautious while treating lithium induced cutaneous side effects for longer duration.

Lithium induced skin lesions could be managed by continuing the same dose and with treating the corresponding lesions as suggested by dermatologist.

We would emphasize caution if patient has pre-existing severe skin lesion before initiating lithium therapy.

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ஒப்புதல் படிவம்

தேதி:

டாக்டர். சுகன்யா பிரியதர்சினி ஆகிய நான். பி.எஸ்.ஜி மருத்துவக் கல்லூரியின் மனநல மருத்துவத் துறையின் கீழ் லித்தியம் உட்கொள்ளும் மன எழுச்சி. மனத்தளர்ச்சி நோயாளிகளின் சரும எதிர்விளைவுகளின் பாதிப்பை அறிய ஆய்வு மேற்கொள்ள உள்ளேன்.

ஏன் ஆய்வு வழிகாட்டி : டாக்டர். ஐ. சையத் உம்மர். உதவி பேராசிரியர்

ஆய்வின் நோக்கம் :.

1. மனத்தளர்ச்சி மன எழுச்சி. நோயாளிகளின் சரும நிகழ்வுகளை மதிப்பிடுதல்
2 லித்தியம் அளவு மற்றும் அதனால் ஏற்படும் சரும பக்க விளைவுகள் அளவை மதிப்பிடுதல்
3 இரத்தத்தில் உள்ள லித்தியம் அளவு மற்றும் அதனால் ஏற்படும் பக்க விளைவுகள் அளவை மதிப்பிடுதல்
4 லித்தியம் சிகிச்சை காலம் மற்றும் சரும பக்க விளைவுகளை மதிப்பிடுதல்
5 லித்தியம் அளவு குறைப்பு மற்றும் நிறுத்துதல் அதனால் ஏற்படும் சரும பக்க விளைவுகள் அளவை மதிப்பிடுதல்
6 லித்தியம் சிகிச்சை ஆரம்பிக்கபட்ட பின் நோயாளியின் ஏற்கனவே இருக்கும் தோல் எதிர்விளைவுகளை மதிப்பிடுதல்

ஆய்வு மேற்கொள்ளும் இடம் :

பி.எஸ்.ஜி மருத்துவமனை. கோயம்புத்தூர்

ஆய்வின் பலன்கள் :

சரும பக்க விளைவுகளின் மதிப்பீடு அதனால் வழக்கமான கண்காணிப்பு. மற்றும் ஆரம்ப நோய் கண்டறிதலினால் மருந்து ஒத்துபோகாமை மற்றும் மனநிலைபாதிப்பை தவிர்த்தல்

லித்தியம் ஆரம்பிக்கப்பட்ட மனதளர்ச்சி. மனஎழுச்சி நோயாளிகளை 6 மாத காலத்திற்கு ஒவ்வொரு மாதமும். 9வது மற்றும் 12வது மாதம் தொடர்ந்து பின்பற்றி சரும பக்க விளைவுகளின் நிகழ்வுகளை காணுதல்.
ஏதேனும் சரும பக்க விளைவுகள் ஏற்பட்டால் மனநல மருத்துவர் மற்றும் தோல் மருத்துவரால் பரிசோதிக்கப்படும். எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு.

ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும். மேலும் இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப்பட்டால் இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியப்படுத்தப்படும்.

ஆய்வாளரின் கையொப்பம் :

தேதி :

ஆய்வுக்குட்படுபவரின் ஒப்புதல் :

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும். விளக்கமாகவும் தெரியப்படுத்தப்படடுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும். இந்த ஆராய்ச்சியின் மருக்துவ ரீதியான குறிப்புகளை வரும் காலத்திலும் உபயோகபடபடுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர். முகவரி :

கையொப்பம் :

தேதி :

உடனிருப்பவரின் கையொப்பம் :

தேதி :

ஆய்வாளரின் தொலைபேசி எண் : 98656 16083

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PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

I , DR. B. S. Suganyapriyadharshini, am carrying out a study on the topic:–Incidence of cutaneous side effects with lithium therapy in BPAD Patients- a prospective cohort study as part of my / our research project being carried out under the Department of PSYCHIATRY

My research guide is: Dr.Syed Ummar

The justification for this study is: Lithium is considered as medication of first choice in BPAD patients. Lithium is known to cause systemic side effects mostly but also cutaneous side effects. The purpose of the study is to evaluate the incidence of cutaneous side effects, whether regular monitoring, early diagnosis and management will help in avoiding the issue of non- compliance and further worsening of mood symptoms.

The objectives of this study are:

1) To assess the incidence of skin reactions in BPAD patients on lithium
2) To evaluate the relationship between dosage of lithium and cutaneous side effects.
3) To assess relationship between serum lithium level and cutaneous side effects
4) To evaluate the duration of lithium therapy and cutaneous side effects

5) To assess the reduction or stoppage of dose of lithium has any change in course of cutaneous side effects, in the departments of Psychiatry .
6) To assess the course of pre-existing skin reactions, when patient is initiated with lithium therapy.

To look for socio-demographic or other variables which may predict the outcome

Sample size: 250

Study volunteers / participants are (specify population group & age group):Patients.Age group is 18 – 60 years

Location: Psychiatry department- PSGIMS&R

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview (specify approximate duration):30-45 minutes.

Data collected will be stored for a period of fifteen years. We will / will not use the data as part of another study.

Health education sessions: Number of sessions: _____. Approximate **duration** of each session:

_____ minutes.

Clinical examination (Specify details and purpose): as part of the Out patient procedure to look for any major co-morbidities needing hospitalized care(exclusion criteria)

Blood sample collection: Specify quantity of blood being drawn: _____ml.

Whether blood sample collection is part of routine procedure or for research (study) purpose: Routine procedure

1. Routine procedure 2. Research purpose

Specify **purpose**, discomfort likely to be felt and side effects, if any: _____

Whether blood sample collected will be stored after study period: Yes / No, it will be destroyed

Whether blood sample collected will be sold: Yes / No

Whether blood sample collected will be shared with persons from another institution: Yes / No

Medication given, if any, duration, side effects, purpose, benefits:

Whether medication given is part of routine procedure: Yes

Whether alternatives are available for medication given: No

Final interview (specify approximate duration):30-45 mts.

Benefits from this study: The purpose of the study is to evaluate the incidence of cutaneous side effects, whether regular monitoring, early diagnosis and management will help in avoiding the issue of non- compliance and further worsening of mood symptoms.

Risks involved by participating in this study: nil

How the **results** will be used:

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me and has been explained to me by the investigators. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date:

Witness:

Contact number of PI: 9566147375

Contact number of Ethics Committee Office: 0422 2570170Extn.: 5818

INITIAL SEMISTRUCTURED PROFORMA

Ip .No	Age	Sex	Socio-economic status	Education	Any Dermatological symptoms	Physical examination for skin reaction	Family H/o skin reaction	Previous skin reaction	Type of skin reaction	Dosage of lithium therapy			Serum lithium level			Duration of lithium therapy			Change of lithium dose			Course of skin reaction		
										<800	800-1200	1200	<0.8	0.8 -1.2	1.2	<6 mon	6 m – 1 yr	>1yr	Reduction	Static	Other MS	Static	Worsen	Improved

FOLLOWUP SEMISTRUCTURED PROFORMA

S. No	Age	Sex	Socio-economic status	Education	Any Dermatological symptoms	Dermatological Opinion	Type of skin reaction	Change in Previous skin reaction	Change in lithium level	Dosage of lithium			Serum lithium level			Duration of lithium therapy			Change of lithium dose			Course of skin reaction		
										<800	800-1200	1200	<0.8	0.8 -1.2	1.2	<6 mon	6 m – 1 yr	>1yr	Reduction	Static	Other MS	Static	Worsen	Improved

SYMPTOM CHECK LIST

1. **Acne:** Lesions may be papulopustular, nodular, or cystic. While acne vulgaris typically consists of comedones.
2. **Acneiform eruptions:** (such as acneiform drug eruptions) have the same characteristic of acne but usually lack comedones.
3. **Psoriasis:** Papulosquamous diseases are characterised by scaling papules (raised lesions <1 cm in diameter) and plaques (raised lesions >1 cm in diameter).
4. **Systemic lupus erythematosis**:

   Malar rash: Fixed erythema flat or raised over the malar eminences, tending to spare the naso labial fold.

   Discoid rash: Erythematous raised patchs with adherent keratotic scaling and follicular Plugging.

5. **Alopecia**
6. **Seborrheic dermatitis:** Red itchy rash with white scales